**To:** Strynar, Mark[Strynar.Mark@epa.gov]; Lindstrom, Andrew[Lindstrom.Andrew@epa.gov]; Medina-Vera, Myriam[Medina-Vera.Myriam@epa.gov]; Biales, Adam[Biales.Adam@epa.gov]; Newton, Seth[Newton.Seth@epa.gov]; McCord, James[mccord.james@epa.gov]; Watkins, Tim[Watkins.Tim@epa.gov]; Orme-Zavaleta, Jennifer[Orme-Zavaleta.Jennifer@epa.gov]; Culpepper, Linda[linda.culpepper@ncdenr.gov]; Allenbach, Becky[Allenbach.Becky@epa.gov]; Smith, Emily J.[Smith.Emily@epa.gov]; Crofton, Kevin[Crofton.Kevin@epa.gov]; Guiseppi-Elie, Annette[Guiseppi-Elie.Annette@epa.gov]; Goode, Teresa[Goode.Teresa@epa.gov]; Oshima, Kevin[Oshima.Kevin@epa.gov]; Tong-Argao, Sania[Tong-Argao.Sania@epa.gov]; Hoffman, Brian[Hoffman.Brian@epa.gov]; Goldfarb, Steven[Goldfarb.Steve@epa.gov]; Grevatt, Peter[Grevatt.Peter@epa.gov]; Behl, Betsy[Behl.Betsy@epa.gov]; Henry, Tala[Henry.Tala@epa.gov]; Raffaele, Kathleen[raffaele.kathleen@epa.gov]; Sinks, Tom[Sinks.Tom@epa.gov]; Grimm, Ann[Grimm.Ann@epa.gov]; Kenneke, John[Kenneke.John@epa.gov]; Maguire, Megan[Maguire.Megan@epa.gov]; Hubbard, Carolyn[Hubbard.Carolyn@epa.gov]; Gilliland, Alice[Gilliland.Alice@epa.gov]; jordan.whichard@nc.gov[jordan.whichard@nc.gov]
**Cc:** Walker, Mary[walker.mary@epa.gov]; Flaherty, Colleen[Flaherty.Colleen@epa.gov]; Johnson, Chris[chris.johnson@ncdenr.gov]; Moore, Zack[zack.moore@dhhs.nc.gov]; Shehee, Mina[mina.shehee@dhhs.nc.gov]; Aubee, Catherine[Aubee.Catherine@epa.gov]; Risen, Amy J[Amy.Risen@dhhs.nc.gov]; Pritchett, Jamie R[Jamie.Pritchett@dhhs.nc.gov]; michael.devito@nih.gov[michael.devito@nih.gov]; Cox, Heidi[heidi.cox@ncdenr.gov]; Kritzer, Jamie[jamie.kritzer@ncdenr.gov]; Zimmerman, Jay[jay.zimmerman@ncdenr.gov]; Grzyb, Julie[julie.grzyb@ncdenr.gov]; Midgette, Robert[robert.midgette@ncdenr.gov]; Holman, Sheila[sheila.holman@ncdenr.gov]; Mclain, Jennifer[Mclain.Jennifer@epa.gov]; Tiago, Joseph[Tiago.Joseph@epa.gov]; Tricas, Marisa[tricas.marisa@epa.gov]; Speth, Thomas[Speth.Thomas@epa.gov]; Burneson, Eric[Burneson.Eric@epa.gov]; Thompkins, Anita[Thompkins.Anita@epa.gov]; Strong, Jamie[Strong.Jamie@epa.gov]; Satterwhite, Dana[dana.satterwhite@ncdenr.gov]; Jessica Godreau[Jessica.godreau@ncdenr.gov]; Lincoln, Larry[Lincoln.Larry@epa.gov]; Campbell-Dunbar, Shawneille[Campbell-Dunbar.Shawneille@epa.gov]; Staley, Danny[Danny.Staley@dhhs.nc.gov]; Kemker, Carol[Kemker.Carol@epa.gov]; Gettle, Jeaneanne[Gettle.Jeaneanne@epa.gov]; Adams, Glenn[Adams.Glenn@epa.gov]; Flowers, Lynn[Flowers.Lynn@epa.gov]; Impellitteri, Christopher[Impellitteri.Christopher@epa.gov]; Scott, Michael[michael.scott@ncdenr.gov]; Tarr, Jeremy M[jeremy.tarr@nc.gov]; Talley, Noelle S[Noelle.Talley@nc.gov]; Karoly, Cyndi[cyndi.karoly@ncdenr.gov]; Gregson, Jim[jim.gregson@ncdenr.gov]; Elizabeth Dittman[Beth.Dittman@dhhs.nc.gov]; Allen, Trent[trent.allen@ncdenr.gov]; Fenton, Suzanne (NIH/NIEHS) [E][suzanne.fenton@nih.gov]; Carroll, Gregory[Carroll.Gregory@epa.gov]; France, Danny[France.Danny@epa.gov]; Mort, Sandra L[sandy.mort@ncdenr.gov]; Grantham, Nancy[Grantham.Nancy@epa.gov]; Lau, Chris[Lau.Christopher@epa.gov]; Munger, Bridget[bridget.munger@ncdenr.gov]; Hines, Erin[Hines.Erin@epa.gov]; Gillespie, Andrew[Gillespie.Andrew@epa.gov]; Hall, Renea[Hall.Renea@epa.gov]; Davis, Molly[Davis.Molly@epa.gov]; Shell, Karrie-Jo[Shell.Karrie-Jo@epa.gov]; Schwartz, Paul[Schwartz.Paul@epa.gov]; Bush, William[Bush.William@epa.gov]; Mancusi-Ungaro, Philip[Mancusi-Ungaro.Philip@epa.gov]; Janovitz, Sara[Janovitz.Sara@epa.gov]; Ravenscroft, John[Ravenscroft.John@epa.gov]; Tilson, Betsey[Betsey.Tilson@dhhs.nc.gov]; Gordon, Scott[Gordon.Scott@epa.gov]; Rubini, Suzanne[Rubini.Suzanne@epa.gov]; Mattas-Curry, Lahne[Mattas-Curry.Lahne@epa.gov]; Young, Sarah[sarah.young@ncdenr.gov]
**From:** Buckley, Timothy
**Sent:** Thur 9/7/2017 12:39:02 PM
**Subject:** RE: Non-Targeted Lab Results Briefing to NC DEQ
NC DEQ nontargeted results f2f RTP report08282017.pdf

Now that our official report has been provided to NC DEQ and Region 4, I am able to share the presentation from our August 28th meeting. Thank you for your patience and understanding.

Tim Buckley

Timothy J. Buckley, PhD

Director of the Exposure Methods & Measurements Division

National Exposure Research Laboratory

109 TW Alexander Drive

Research Triangle Park, NC 27711

Email: buckley.timothy@epa.gov

URL: http://www.epa.gov/heasd/staff/buckley.html

Phone: (919) 541-2454 (O); FAX: -0239

-----Original Appointment-----
**From:** Buckley, Timothy
**Sent:** Monday, August 14, 2017 2:19 PM
**To:** Buckley, Timothy; Strynar, Mark; Lindstrom, Andrew; Medina-Vera, Myriam; Biales, Adam; Newton, Seth; McCord, James; Watkins, Tim; Orme-Zavaleta, Jennifer; Culpepper, Linda; Allenbach, Becky; Smith, Emily J.; Crofton, Kevin; Guiseppi-Elie, Annette; Goode, Teresa; Oshima, Kevin; Tong-Argao, Sania; Hoffman, Brian; Goldfarb, Steven; Grevatt, Peter; Behl, Betsy; Henry, Tala; Raffaele, Kathleen; Sinks, Tom; Ann Grimm; Kenneke, John; Maguire, Megan; Carolyn Hubbard; Gilliland, Alice; jordan.whichard@nc.gov
**Cc:** Walker, Mary; Flaherty, Colleen; Johnson, Chris; Moore, Zack; Shehee, Mina; Aubee, Catherine; Risen, Amy J; Pritchett, Jamie R; michael.devito@nih.gov; Cox, Heidi; Kritzer, Jamie; Zimmerman, Jay; Grzyb, Julie; Midgette, Robert; Holman, Sheila; Mclain, Jennifer; Tiago, Joseph; Tricas, Marisa; Speth, Thomas; Burneson, Eric; Thompkins, Anita; Strong, Jamie; Satterwhite, Dana; Godreau, Jessica; Lincoln, Larry; Campbell-Dunbar, Shawneille; Staley, Danny; Kemker, Carol; Gettle, Jeaneanne; Adams, Glenn; Flowers, Lynn; Impellitteri, Christopher; Scott, Michael; Tarr, Jeremy M; Talley, Noelle S; Karoly, Cyndi; Gregson, Jim; Dittman, Elizabeth; Allen, Trent; Fenton, Suzanne (NIH/NIEHS) [E]; Carroll, Gregory; France, Danny; Mort, Sandra L; Grantham, Nancy; Christopher Lau; Munger, Bridget; Hines, Erin; Andrew Gillespie; Hall, Renea; Davis, Molly; Shell, Karrie-Jo; Schwartz, Paul; Bush, William; Mancusi-Ungaro, Philip; Janovitz, Sara; Ravenscroft, John (Ravenscroft.John@epa.gov); Tilson,

Betsey; Gordon, Scott; Rubini, Suzanne; Detlef knappe; Mattas-Curry, Lahne; Young, Sarah
**Subject:** Non-Targeted Lab Results Briefing to NC DEQ
**When:** Monday, August 28, 2017 9:00 AM-12:00 PM (UTC-05:00) Eastern Time (US & Canada).
**Where:** EPA RTP C111A-B; Agenda attached.

The primary goal of this briefing is to communicate lab results to NC DEQ and address their questions. Becky Allenbach in Region 4 and Linda Culpepper NC DEQ will extend invitation to others in their organization as appropriate. I am expanding invite list to include other labs and Centers and EPA Program Offices with potential interest.

A webinar link has been provided for remote access.

http://epawebconferencing.acms.com/ /

Conference Number:

Conference Code:

**To:** Allison, Rose[Allison.Rose@epa.gov]; Doa, Maria[Doa.Maria@epa.gov]; Krasnic, Toni[krasnic.toni@epa.gov]; EL-Zoobi, Majd[El-Zoobi.Majd@epa.gov]; Aubee, Catherine[Aubee.Catherine@epa.gov]; Vendinello, Lynn[Vendinello.Lynn@epa.gov]; kemper.carol@epa.gov[kemper.carol@epa.gov]; Tobias, David[Tobias.David@epa.gov]; Benson, Amy[Benson.Amy@epa.gov]; George, Verne[George.Verne@epa.gov]; Mitchell, Ken[Mitchell.Ken@epa.gov]; sheila.holman@ncdenr.gov[sheila.holman@ncdenr.gov]; linda.culpepper@ncdenr.gov[linda.culpepper@ncdenr.gov]; Toney, Anthony[Toney.Anthony@epa.gov]; Bookman, Robert[Bookman.Robert@epa.gov]; Banister, Beverly[Banister.Beverly@epa.gov]
**Cc:** JOHNSON, MICHAEL E[MICHAEL.E.JOHNSON@chemours.com]
**From:** O'KEEFE, KATHLEEN E
**Sent:** Wed 7/12/2017 8:16:58 PM
**Subject:** Chemours web conference instructions Thursday July 13 at 1:00 pm

The web conference instructions are below. Please note you can join 10 minutes prior to the start of the meeting. After you register an access link will be provided by AT&T.

Thanks, Kathy

**Kathleen O'Keefe**
Chemours Product Sustainability Director

Mobile

Your web conference has been scheduled.

**Title**: Chemours Web Conference

**Date**: Thursday, July 13, 2017

**Time**: 1:00 PM - 2:00 PM Eastern Time

## Participant Instructions

**Web Link:** A participant may register for the conference at after which s/he will receive an email containing a personalized access link.

**To:** Risen, Amy J[Amy.Risen@dhhs.nc.gov]; Audra Henry[ate1@cdc.gov]; Wheeler, John[Wheeler.John@epa.gov]; Mitchell, Ken[Mitchell.Ken@epa.gov]; Strong, Jamie[Strong.Jamie@epa.gov]; Henry, Tala[Henry.Tala@epa.gov]; Behrsing, Tracy[behrsing.tracy@epa.gov]; Benson, Amy[Benson.Amy@epa.gov]; Aubee, Catherine[Aubee.Catherine@epa.gov]; Kemker, Carol[Kemker.Carol@epa.gov]; Allenbach, Becky[Allenbach.Becky@epa.gov]; Doa, Maria[Doa.Maria@epa.gov]; Mort, Sandra L[sandy.mort@ncdenr.gov]; Shehee, Mina[mina.shehee@dhhs.nc.gov]; Elizabeth Dittman[Beth.Dittman@dhhs.nc.gov]; Holt, Kennedy[Kennedy.Holt@dhhs.nc.gov]; Langley, Rick[rick.langley@dhhs.nc.gov]; connie.brower@ncdenr.gov[connie.brower@ncdenr.gov]; Culpepper, Linda[linda.culpepper@ncdenr.gov]; Holloway, Tracey S[Tracey.Holloway@ncdenr.gov]; Donohue, Joyce[Donohue.Joyce@epa.gov]
**Cc:** Tina Forrester[txf5@cdc.gov]; Susan Moore[sym8@cdc.gov]; Selene Chou[cjc3@cdc.gov]; Trent LeCoultre[tll7@cdc.gov]; idz7@cdc.gov[idz7@cdc.gov]
**From:** Behl, Betsy
**Sent:** Fri 7/7/2017 10:34:24 PM
**Subject:** RE: GenX Risk Assessment Knowledge Gaps

A few minor clarifications below (it was hard to know who was speaking on the phone)

**From:** Risen, Amy J [mailto:Amy.Risen@dhhs.nc.gov]
**Sent:** Friday, July 07, 2017 6:17 PM
**To:** Audra Henry <ate1@cdc.gov>; Wheeler, John <Wheeler.John@epa.gov>; Mitchell, Ken <Mitchell.Ken@epa.gov>; Behl, Betsy <Behl.Betsy@epa.gov>; Strong, Jamie <Strong.Jamie@epa.gov>; Henry, Tala <Henry.Tala@epa.gov>; Behrsing, Tracy <behrsing.tracy@epa.gov>; Benson, Amy <Benson.Amy@epa.gov>; Aubee, Catherine <Aubee.Catherine@epa.gov>; Kemker, Carol <Kemker.Carol@epa.gov>; Allenbach, Becky <Allenbach.Becky@epa.gov>; Doa, Maria <Doa.Maria@epa.gov>; Mort, Sandra L <sandy.mort@ncdenr.gov>; Shehee, Mina <mina.shehee@dhhs.nc.gov>; Elizabeth Dittman <Beth.Dittman@dhhs.nc.gov>; Holt, Kennedy <Kennedy.Holt@dhhs.nc.gov>; Langley, Rick <rick.langley@dhhs.nc.gov>; connie.brower@ncdenr.gov; Culpepper, Linda <linda.culpepper@ncdenr.gov>; Holloway, Tracey S <Tracey.Holloway@ncdenr.gov>; Donohue, Joyce <Donohue.Joyce@epa.gov>
**Cc:** Tina Forrester <txf5@cdc.gov>; Susan Moore <sym8@cdc.gov>; Selene Chou <cjc3@cdc.gov>; Trent LeCoultre <tll7@cdc.gov>; idz7@cdc.gov
**Subject:** RE: GenX Risk Assessment Knowledge Gaps

Thank you to everyone for providing feedback on our risk assessment for GenX. I'm providing a summary below, which includes points of contact to follow up with. Questions 1-4 were posed by DHHS before the call as main talking points. Text in blue is a summary of the comments. NC DHHS makes every attempt to follow the approach used by the EPA when doing risk assessments. Therefore, we have underlined blue text as take home messages that DHHS will be applying to the GenX risk assessment for NC residents using drinking water originally referenced in Sun et al 2016.

DHHS intends to respond to the public with a new drinking water level and health guidance early in the week of July 10th. We are hopeful that you will be able to provide feedback on cancer and fish consumption ASAP; please see number 5 below for details. I am also interested in data we discussed on interspecies kinetics differences.

Thanks again!

Amy

1) **Animal toxicity studies and the point of departure (POD):** Sufficient data was available to lower the POD NOAEL to 0.1 mg/kg/day (subchronic toxicity test OECD 407 with mice). An uncertainty factor of 10 will be applied for subchronic to chronic extrapolation

**a.** **We have consensus that the POD of will also be used by the EPA Risk Assessment Division (RAD) for risk assessment of GenX.**

b. requested that toxicological effects and endpoint descriptions be strengthened so we can be more specific about the effects associated with NOAELs and PODs that are referenced during the risk assessment.

c. It was noted that PODs on the ECHA dossier are selected and reported by chemical manufacturer rather than the ECHA.

2) **Routes of exposure and the relative source contribution (RSC):** People may be exposed to GenX through routes other than drinking water. The typical value used for RSC in risk assessment of organic chemicals is 0.2, and this is the value used by the EPA for their evaluation of PFOA and PFOS drinking water health advisories. **We request guidance from the EPA and ATSDR on the use of an RSC of 0.2.**

a. EPA RAD has not evaluated RSC for drinking water exposures to GenX because drinking water was not previously thought to be a route of exposure to this chemical.

b. EPA OST ~~RAD~~ did use 20% RSC for PFOA and PFOS due to ubiquitous presence in the environment and uncertainty about amounts of these chemicals reaching people through the different exposure routes.

c. EPA OST ~~RAD~~ uses 100% RSC when looking at exposures to the infant age group.

**d.** **DHHS intends to use 20% RSC based on the EPA decision tree for deriving water quality criteria (EPA-822-B-00-004) and apply the exposure to children birth to <6years using exposure factors from the new EPA RAGS supplement (OSWER Directive 9200.1-120).**

3) **Risk assessment method and interspecies uncertainty factor**: The default value for interspecies variability of 10 is likely to underestimate the toxicity of GenX to humans. We present the EPA method used to extrapolate a human equivalent dose (HED) for PFOA and PFOS in this document. Interspecies uncertainty modeling for PFOA and PFOS yielded a calculated factor of 140 to 710X for kinetics differences and an additional 3X was allocated for other variability across species. The total uncertainty accounted for across species by EPA for PFOA and PFOS was calculated by DHHS and the maximum was 2,100X. **We also request guidance from the EPA and ATSDR on an appropriate interspecies uncertainty factor for GenX.**

**a.** **DHHS understands that EPA RAD currently intends to use a for their risk assessment for the consent order for GenX manufacturing**

b. EPA: While human PFOS & PFOA clearance rates are slower in humans than test animals, interspecies kinetics variability is not expected to occur at the same magnitude for GenX. The supporting information comes from a comparison of the clearance rates for branched vs linear PFOAs, in which branched isomers are cleared faster; GenX is branched and so would be predicted to clear faster.

i. DHHS requests references on comparison of branched vs linear PFOAs, renal transfer proteins used, and any additional information helpful in reviewing the prediction of the interspecies variability expected for GenX. Follow up discussions will go through Joyce Donohue, Catherine Aubree, and Jaime Strong as points of contact.

c. Additional UFs were discussed, including the subchronic to chronic extrapolation. EPA RAD does not use a $UF_{Subchronic\text{-}Chronic}$ as part of its typical procedure. DHHS explained our goal to be protective of public health over a lifetime of exposure. EPA explained that **EPA IRIS procedure does focus more on lifetime exposures and their risk assessment does add in a $UF_{Subchronic\text{-}Chronic}$ of 10**.

d. Questions were raised regarding EPA's current review of the GenX consent order and associated risk assessment; now that a release to a water source is known, will the risk assessment include a public drinking water level?

4) **Drinking water concentration guidance for other PFECAs:** The Sun et al 2016 publication identified not only GenX, but also other perfluoroalkyl ether carboxylic acids

(PFECAs) present in the Cape Fear River and local drinking water in 2013 and 2014. Quantification of the concentrations of other PFECAs was not possible due to the lack of analytical chemistry standards, however some PFECAs may have been present at concentrations 15 times higher than GenX. Presumed high concentrations are prompting questions about drinking water safety, however no toxicity data is available for these PFECAs. **We request guidance from the EPA and ATSDR on a health protective drinking water value that can be provided to residents of this community. Would it be appropriate to use the PFOA + PFOS health advisory of 70 ng/L?**

a. Maria Doa and Catherine Aubree will review the PFECAs chemical structures to see if general advice can be given on how much we can read across health concerns from PFOA and PFOS. It is not within the scope of their work on GenX to review PFECAs at this time and it is understood that guidance along these lines may be limited. Amy Risen will provide the supplemental document for Sun et al to clarify the PFECAs in question.

5) Additional questions raised in call

a. Fish Consumption:

i. DHHS: The public is asking about safety of fish consumption. Can the EPA make any recommendations?

ii. EPA: The EPA does not expect GenX to bioaccumulate. There is some data on concentrations in fish from documents that are confidential, as well as some non-confidential data.

1. The DHHS spoke with ' after the call for clarification. She explained that the BCF reported by Hoke et al 2016 is low enough as to not typically warrant additional fish consumptions studies. EPA will follow up Monday with a statement with the appropriate caveats for the unknowns of emerging chemicals and limited data.

b. Cancer Risk Assessment:

i. DHHS: The public is concerned about the risk of cancer from GenX. We have limited data, but can the EPA suggest a way to convey the risk of cancer?

ii. EPA: Joyce Donohue will review the raw data from OECD 453 to determine if the notes on the rate of occurrence for liver necrosis are sufficient to calculate a risk. Amy Risen will provide the raw data, which had been provided by Chemours. Amy also has raw data for OECD 407 GenX testing for rats & mice, if needed by anyone in the group.

**From:** Risen, Amy J
**Sent:** Wednesday, July 05, 2017 7:38 PM
**To:** 'Audra Henry' <ate1@cdc.gov>; 'John Wheeler' <Wheeler.John@EPA.gov>; 'mitchell.ken@epa.gov' <mitchell.ken@epa.gov>; 'Behl.betsy@epa.gov' <Behl.betsy@epa.gov>; 'Strong.jamie@epa.gov' <Strong.jamie@epa.gov>; 'Henry.tala@epa.gov' <Henry.tala@epa.gov>; 'Behrsing.tracy@epa.gov' <Behrsing.tracy@epa.gov>; 'Benson.amy@epa.gov' <Benson.amy@epa.gov>; 'Aubee.catherine@epa.gov' <Aubee.catherine@epa.gov>; 'Kemker.carol@epa.gov' <Kemker.carol@epa.gov>; 'Allenbach.becky@epa.gov' <Allenbach.becky@epa.gov>; 'Doa, Maria' <Doa.Maria@epa.gov>; Mort, Sandra L <sandy.mort@ncdenr.gov>; Shehee, Mina <mina.shehee@dhhs.nc.gov>; Dittman, Elizabeth <Beth.Dittman@dhhs.nc.gov>; Holt, Kennedy <Kennedy.Holt@dhhs.nc.gov>; Langley, Rick <rick.langley@dhhs.nc.gov>; Brower, Connie <connie.brower@ncdenr.gov>
**Cc:** 'Tina Forrester' <txf5@cdc.gov>; 'Susan Moore' <sym8@cdc.gov>; 'Selene Chou' <cjc3@cdc.gov>; 'Trent LeCoultre' <tll7@cdc.gov>; 'Rachel Worley' <idz7@cdc.gov>
**Subject:** GenX Risk Assessment Knowledge Gaps

Hello everyone!

NC DHHS has been discussing GenX with both EPA and ATSDR and we really appreciate the help you've been giving us. We'll be holding a conference call tomorrow to talk about the progress we've made on our GenX risk assessment, and talk about knowledge gaps. We'll be asking for rapid feedback within the next week to help inform our risk communications with the public.

I've attached a document for you to review with requests for feedback bolded in purple.

Thanks so much and talk to you all tomorrow!

**Amy Risen, PhD**

Environmental Toxicologist

Division Public Health, Occupational and Environmental Epidemiology

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Raleigh, NC 27699-1912




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**Initial Calculation of a Provisional Health Screening Level for GenX in drinking water from the Cape Fear River.**

Upon learning of the media reports of GenX occurring in drinking water, DHHS responded to urgent inquiries about health effect data for this compound. To bring context to the concentrations of GenX reported to be in drinking water in 2013 and 2014, DHHS initially calculated a provisional drinking water level that corresponded to a Derived No Effect Level for humans for oral exposure published by the European Chemical Agency (ECHA). The initial response process is outlined below.

1) In the absence of health guidance values published by organizations in the U.S., we used documentation from Europe. A Derived No Effect Level (DNEL) for humans for oral exposure was taken from the European Chemical Agency (ECHA) website (CAS:62037-80-3). https://echa.europa.eu/registration-dossier/-/registered-dossier/2679/7/1

2) DNEL for humans was calculated by ECHA.:
    a. NOAEL= 1.0 mg/kg bw/day (2-year chronic tox & cancer study)
    b. Total uncertainty factor of 100
        i. Interspecies variability=10
        ii. Intraspecies variability=10
    c. DNEL=(1.0 mg/kg bw/day)/100= 0.01mg/kg/day



3) DHHS applied exposure factors using ATSDR exposure dose guidelines. A drinking water concentration that corresponds to ECHA's DNEL was determined based on the calculation of Concentration= Dose*Body Weight/Intake. The values used for body weight and drinking water intake account for the large amount of water that bottle-fed infants consume in relation to their low body weight. There was an assumption that 100% of the dose was coming from water.
    a. The ATSDR guideline accounts for the large amount of water bottle-fed infants consume in relation to their low body weight.
        i. Dose=0.01 mg/kg bw/day
        ii. Body Weight=7.8 kg
        iii. Intake=1.1 L/day
        iv. Concentration=(0.01 mg/kg/day)*7.8kg/(1.1L/day)=**71,000 ng/L**

4) We used 71,000 ng/L as a provisional health screening value, and now we are seeking guidance on appropriate revisions.

**Moving forward:**

After calculating this initial value, DHHS identified specific information about GenX that requires modifications and special considerations for risk assessment. These considerations are described in the remainder of this document.

**DHHS is currently reviewing our provisional health screening level of 71,000 ng/L and seeking input from the ATSDR and EPA.**

Four risk assessment considerations are listed below for GenX. EPA has already provided feedback in agreement of using the POD of 0.1 mg/kg/day. Input is still required on the remaining three considerations.

1) **Animal toxicity studies and the point of departure (POD):** Sufficient data was available to lower the POD NOAEL to 0.1 mg/kg/day (subchronic toxicity test OECD 407 with mice). An uncertainty factor of 10 will be applied for subchronic to chronic extrapolation

2) **Routes of exposure and the relative source contribution (RSC):** People may be exposed to GenX through routes other than drinking water. The typical value used for RSC in risk assessment of organic chemicals is 0.2, and this is the value used by the EPA for their evaluation of PFOA and PFOS drinking water health advisories. We request guidance from the EPA and ATSDR on the use of an RSC of 0.2.

3) **Risk assessment method and interspecies uncertainty factor**: The default value for interspecies variability of 10 is likely to underestimate the toxicity of GenX to humans. We present the EPA method used to extrapolate a human equivalent dose (HED) for PFOA and PFOS in this document. Interspecies uncertainty modeling for PFOA and PFOS yielded a calculated factor of 140 to 710X for kinetics differences and an additional 3X was allocated for other variability across species. The total uncertainty accounted for across species by EPA for PFOA and PFOS was calculated by DHHS and the maximum was 2,100X. We also request guidance from the EPA and ATSDR on an appropriate interspecies uncertainty factor for GenX.

4) **Drinking water concentration guidance for other PFECAs:** The Sun et al 2016 publication identified not only GenX, but also other perfluoroalkyl ether carboxylic acids (PFECAs) present in the Cape Fear River and local drinking water in 2013 and 2014. Quanfication of the concentrations of other PFECAs was not possible due to the lack of analytical chemistry standards, however some PFECAs may have been present at concentrations 15 times higher than GenX. Presumed high concentrations are prompting questions about drinking water safety, however no toxicity data is available for these PFECAs. We request guidance from the EPA and ATSDR on a health protective drinking water value that can be provided to residents of this community. Would it be appropriate to use the PFOA + PFOS health advisory of 70 ng/L?

## 1) Test animal toxicity data and the point of departure (POD)

Since the initial assessment, DHHS reviewed the available toxicity studies on GenX to determine an appropriate POD (Table 1). Review of the NOAELs is also helpful for demonstrating the interspecies variability referenced in the next section.

**Methods in data collection:**

- ~ OECD standardized studies were submitted during chemical registration in Europe and summaries of the findings are published on the European Chemical Agency (ECHA) Website. Studies on the ECHA website were included in our review if the exposure duration was sub-chronic or chronic. ECHA also reports extra studies provided to them. However these extra studies lacked method details and were not included in our review.
- ~ We also looked for other peer reviewed studies and only found four on toxicity. Two articles restate chemical registration studies shown on ECHA and so were not added to the table below (Gannon et al 2016 Toxicology, Rae et al 2015 Toxicology Reports). One study was an ecological risk assessment so was not included (Hoke et al 2016 Chemosphere). Rushing et al 2017 *Evaluation of the Immunomodulatory Effects of (GenX) in C57BL/6 Mice* was a new study and so was included in our evaluation.

**Table 1: Subchronic and chronic toxicity studies with GenX**

| Method | Lowest NOAEL in Study | NOAELs |
|---|---|---|
| *Studies* | | |
| **Repeated dose toxicity** | | |
| Oral | | |
| OECD 407: 28-Day Oral Tox in Rodents (Rats) | 30 mg/kg bw/day | 30 mg/kg bw/day (male)<br>300 mg/kg bw/day (female) |
| OECD 407: 28-Day Oral Tox in Rodents (Mice) | 0.1 mg/kg bw/day | 0.1 mg/kg bw/day (male)<br>3 mg/kg bw/day (female) |
| OECD 408: 90-Day Oral Tox in Rodents (Rats) | 10 mg/kg bw/day | 10 mg/kg bw/day (male)<br>100 mg/kg bw/day (female) |
| OECD 408: 90-Day Oral Tox in Rodents (Mice) | 0.5 mg/kg bw/day | 0.5 mg/kg bw/day (M&F) |
| OECD 453: 2-yr Combined Chronic Toxicity & Carcinogenicity (Rats) | 1 mg/kg bw/day | 1 mg/kg bw/day (male)<br>50 mg/kg bw/day (female) |
| | | |
| Carcinogenicity | | |
| ** findings are from same experimental trials as reported on to rU.E.L.U. 453 above.*<br>OECD 453: 2-yr Combined Chonic Toxicity & Carcinogenicity (Rats) | 1 mg/kg bw/day | 1 mg/kg bw/day (male)<br>50 mg/kg bw/day (female) |
| | | |
| **Toxicity to reproduction** | | |
| Toxicitity to reproduction | | |
| OECD 421: Reproduction/Developmental Tox Screen (Mice) | 0.1 mg/kg bw/day | 0.1 mg/kg bw/day (FO male)<br>0.5 mg/kg bw/day (FO female)<br>0.5 mg/kg bw/day (Offspring)<br>5 mg/kg bw/day (Reproductive Toxicity) |
| Developmental toxicity/teratogenicity | | |
| OECD 414: Prenatal Developmental Tox (Rats) | 10 mg/kg bw/day | 10 mg/kg bw/day (Maternal)<br>10 mg/kg bw/day(Offspring) |
| *Additional peer-reviewed studies* | | |
| Rushing et al 2017. Evaluation of immunomodulatory effects of GenX in mice. Toxicol. Sci. 156(1):179-189 | 1 mg/kg/day | 1 mg/kg/day (M&F) |

**Comparison of NOAELs, including interspecies variability and sex-specific differences**

The 28-day study's lowest NOAEL for mice was two orders of magnitude lower than that for rats, and NOAELs for males were one order of magnitude lower than those for females. Similar trends are seen in the 90-day studies, where mice were more sensitive than rats (by one to two orders of magnitude) and male rats were more sensitive than female rats (by one order of magnitude). Effects on the liver were the primary endpoints noted in these subchronic studies, and the lowest NOAELs were 0.5 and 0.1 mg/kg/day in the mice studies.

The 2-year chronic toxicity and carcinogenicity study used rats, and both carcinogenic and liver endpoints had NOAELs of 1.0 mg/kg/day. A 2-year chronic mouse study was not conducted. Two studies were conducted on reproduction and development. OECD 421 used mice, while OECD 414 used rats. Once again we see two orders of magnitude between the species' NOAELs with the lowest mouse NOAEL at 0.1 mg/kg/day. It is of interest to note that the lowest NOAEL for offspring (with dosing occurring to the parental generation only) was 0.5 mg/kg/day for system toxicity to both males and females in the F1 generation. One additional study was found in the peer reviewed literature that used mice to study immunological effects. The lowest NOAELs were 1.0 mg/kg/day.

**Caveats for old POD:** There are caveats regarding the cancer and chronic study because the most sensitive rodent was not tested. The reported NOAEL of 1.0 mg/kg/day is likely to underestimate chronic and carcinogenic toxicity compared to the subchronic tests submitted, and therefore is not the most protective POD. Three of the seven subchronic studies for GenX have NOAELS in the range of 0.1-0.5 mg/kg bw/day. These studies are subchronic and would therefore be subject to modification by an uncertainty factor of 10.



**Selection of new POD:** We find sufficient support to lower our initial POD of 1.0 mg/kg/day. The revised POD will be a NOAEL of 0.1 mg/kg/day for subchronic toxicity to mice (OECD 407). The same POD was selected by both RIVM and EPA when reviewing these GenX toxicity studies (RIVM 2016, EPA 2008).

**Caveat for cancer risk assessment**: The chronic toxicity and carcinogenicity study has caveats because the most sensitive species (mice) was not tested. Closer review of the study also reveals that control animals had high background levels of interstitial cell adenomas and hyperplasia (data summarized in table A4 of RIVM Letter 2016). These observations raise questions about QA/QC and test data validity. In addition, we currently lack sufficient data to calculate a slope factor for GenX and are unable to conduct a cancer risk assessment.

**Observation of high interspecies variability in reponse to GenX:** It is also important to notice the trend that these limited test results are showing for interspecies variability and sex-specific differences. GenX is a perfluorinated alkyl substance, as are more well studied chemicals perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). PFOS and PFOA are known to have high interspecies variability and sex-specific differences for chemical clearance rates and toxicity endpoints (EPA 2016a, 2016b). High interspecies variability is an important consideration in the risk assessment process, as will be further discussed in the next section.

## An interspecies uncertainty factor for GenX

### Rationale for using high interspecies variability uncertainty factor for GenX

GenX is a member of a chemical group called per- and polyfluorinated alkyl substances (PFASs). Perfluorooctanoic Acid (PFOA) and perfluorooctane sulfonate (PFOS) are among the better studied PFASs. The US EPA has established a non-regulatory drinking water health advisory (HA) for the total concentration of PFOA and PFOS of 70 ng/L (EPA 2016a, 2016b)). There is a wealth of peer reviewed environmental and human health data available for PFOA and PFOS, including animal studies and epidemiological studies with humans. The availability of a risk assessment from an authoritative agency provides a relevant model to evaluate for considerations specific to this class of chemicals.

High interspecies variability is a major consideration in the EPA risk assessment of PFOA and PFOS. High interspecies variability (up to 300X) is seen in the limited rodent studies available on GenX. Similar interspecies and sex-specific toxicity trends can been seen in GenX and other PFASs. Taken together, this warrants departure from the default of 10X for interspecies uncertainty in the risk assessment of GenX.

### High interspecies variability approach used for PFOA & PFOS

Risk assessments often default to using a value of 10 for assessing interspecies variability in toxicokinetics and toxicodynamics (Rhomberg & Lewandowski 2004). Toxicokinetics are the affect of the body on the chemical, such as adsorption, distribution, metabolism, and excretion. Toxicodynamics are the affect of the chemical on the body, such as impacts on a target molecule or organ.

Animals used for laboratory testing have been shown to remove PFOA and PFOS from their bodies at a rate that is faster than humans do. For example, humans in two epidemiological studies were found to have PFOA half lives of 2.8 and 3.8 years on average (EPA 2016b). In contrast, PFOA half lives measured in monkeys, rats, and mice ranged from 3.4 hours to 30 days (EPA 2016b). The mechanisms for these differences are complex and the reader is refered to the PFOA and PFOS drinking water HA documents for details.

The EPA HA risk assessments for PFOA and PFOS address kinetic differences by modeling a human equivalent dose (HED) via modeled animal blood serum concentrations. The EPA's modeling yielded HED values that were between 140 and 710 times smaller than the NOAELs from the test animals (Table 2). The HEDs accounted for the majority of the interspecies variability, and an additional interspecies variability uncertainty factor of 3 was multiplied by the HED to account for remaining differences. The total interspecies variability accounted for ranged from 420 to 2,100 (Table 3). For comparison see the 2016 RIVM report letter, in which interspecies variability is broken down into 66 for kinetics and 1.8 for other (Table 5).

| Table 2: Magnitude of Difference Between NOAELs and Modeled HED Values for PFOA and PFOS Drinking Water Health Advisories | | | |
|---|---|---|---|
| References for NOAELs and LOAELs for PFOS and PFOA | NOAEL | HED | *Calculated NOAEL/HED |
| PFOS | | | |
| Seacat et al 2003 | 0.34 | 0.0013 | 260 |
| Luebker et al 2005b | 0.1 | 0.00051 | 200 |
| Luebker et al 2005a | 0.4 | 0.0016 | 250 |
| Butenhoff et al 2009 | 0.3 | 0.00084 | 360 |
| Lau et al 2003 | 1.0 | 0.0014 | 710 |
| PFOA | | | |
| Palazzolo et al 1993 & Perkins et al 2004 | 0.64 | 0.0044 | 140 |
| DeWitt et al 2008 | 1.88 | 0.0053 | 360 |
| NOAEL: No Observed Adverse Effect Level; HED: Human Equivalent Dose. | | | |
| NOAEL and HED values came from EPA PFOA and PFOS drinking water health advisory development documents. | | | |
| *Calculated NOAEL/HED values were calculated by DHHS. | | | |
| While NOAEL values were sometimes provided with one significant digit, EPA calculations consistently provided HEDs with two significant digits. Our calculations of NOAEL/HED are also reported in two significant digits. | | | |

### Selection of an interspecies uncertainty factor for GenX

NC DHHS does not have the expertise to determine how large the interspecies uncertainty factor should be for GenX. However, we can calculate drinking water levels for GenX using different potential uncertainty factors in order to gain insight on the possible range of values that should be considered. DHHS compared drinking water concentrations calculated with a default interspecies variability (10) and the maximum calculated PFOA and PFOS interspecies variability value (2,100) (Table 4). This provides a range of theoretical health protective GenX drinking water concentrations between 140 and 0.7 ng/L. These theoretical health protective drinking water concentrations are lower than the average concentrations of GenX (631ng/L) found in the Cape Fear River in 2013 and 2014 (Sun et al 2016). DHHS is seeking guidance from EPA and ATSDR on the selection and/or development of an appropriate interspecies uncertainty factor for GenX.

| Table 3: Uncertainty Factors Accounted for in PFOA and PFOS Drinking Water Health Advisories | | | | | | | |
|---|---|---|---|---|---|---|---|
| **References for NOAELs and LOAELs for PFOS and PFOA** | **NOAEL** | **Interspecies Variability** | | | **Intra species Variability** | **Subchronic to Chronic** | ***Total UF** |
| | | *Calculated NOAEL/HED | Other | *Total | | | |
| PFOS | | | | | | | |
| Seacat et al 2003 | 0.34 | 260 | 3 | **780** | **10** | | **7,800** |
| Luebker et al 2005b | 0.1 | 200 | 3 | **600** | **10** | | **6,000** |
| Luebker et al 2005a | 0.4 | 250 | 3 | **750** | **10** | | **7,500** |
| Butenhoff et al 2009 | 0.3 | 360 | 3 | **1,100** | **10** | | **11,000** |
| Lau et al 2003 | 1.0 | 710 | 3 | **2,100** | **10** | | **21,000** |
| PFOA | | | | | | | |
| Palazzolo et al 1993 & Perkins et al 2004 | 0.64 | 140 | 3 | **420** | **10** | | **4,200** |
| DeWitt et al 2008 | 1.88 | 360 | 3 | **1,100** | **10** | **10** | **11,000** |
| NOAEL: No Observed Adverse Effect Level; HED: Human Equivalent Dose; UF:Uncertainty Factor. | | | | | | | |
| NOAEL and HED values came from EPA PFOA and PFOS drinking water health advisory development documents. | | | | | | | |
| *Values calculated by DHHS based on using NOAEL/HED for an additional interspecies uncertainty factor. | | | | | | | |
| While NOAEL values were sometimes provided with one significant digit, EPA calculations consistently provided HEDs with two significant digits. DHHS calculations are also reported in two significant digits. | | | | | | | |



| Table 4: Use of PFOA & PFOS Interspecies Uncertainty to Calculate Possible Health Protective Drinking Water Concentrations | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | NOAEL (mg/kg/day) | Uncertainty Factors (UFs) | | | | RfD (mg/kg/day) | DWEL (mg/L) | Drinking Water Concentration (mg/L) | Drinking Water Concentration (ng/L) |
| | | *Possible Inter species Variability | Intra species Variability | Subchronic to Chronic | Total UF | | | | |
| OECD 407 Subchronic Mice | 0.1 | 10 | 10 | 10 | 1,000 | 0.0001000 | 0.00071 | 0.00014 | 140 |
| with GenX | 0.1 | 2,100 | 10 | 10 | 210,000 | 0.0000005 | 0.000003 | 0.0000007 | 0.7 |
| * Possible Interspecies Variability=Comaprison of defaut value of 10 with maximum PFOA and PFOS calculated interspecies uncertainty factor from Table 3 (2,100). | | | | | | | | | |
| Reference Dose=RfD=NOAEL/Total UF | | | | | | | | | |
| Drinking Water Equivalent Level=DWEL=RfD*BW/DWI. Bodyweight=BW. Drinking water intake=DWI. BW=7.8kg and DWI=1.1L/day for infants per ATSDR guidelines | | | | | | | | | |
| Drinking Water Concentration=DWEL*RSC. Relative Source Contribution=RSC=20% | | | | | | | | | |

**Table 5: Comparison of PODs and UFs used by other agencies to obtain a reference dose tolerated by humans**

| | | EPA PFOA & PFOS Health Advisories | | ECHA | | RIVM | | EPA 2008 Consent Order | | WV DEP Consent Order | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PFOA & PFOS (mg/kg/day) | UFs | GenX (mg/kg/day) | UFs | GenX (mg/kg/day) | UFs | GenX (mg/kg/day) | UFs | GenX (mg/kg/day) | UFs |
| PODs | NOAEL | 0.1-1.88 | | 1.0 | | 0.1 | | 0.1 | | 0.1 | |
| | | | | | | | | | | | |
| Uncertainty Factors (UFs) | Interspecies Variability (Total) | | *420-2,100 | | 10 | | *120 | | 10 | | 10 |
| | Intraspecies Variability | | 10 | | 10 | | 10 | | 10 | | - |
| | LOAEL to NOAEL Extrapolation | | **10 | | - | | - | | - | | - |
| | Subchronic to Chronic Extrapolation | | **10 | | - | | - | | - | | 10 |
| | Total Uncertainty Factor | | 4,200-21,000 | | 100 | | 1,200 | | 100 | | 100 |
| | | | | | | | | | | | |
| | Final reference dose for humans | 0.00002 | | 0.01 | | - | | 0.001 | | 0.001 | |



Values used by the EPA to for PFOA and PFOS are shown in ranges because a variety of calculations were compared by the EPA before selecting the most protective value.

*Interspecies variability (total) was calculated by DHHS from multiple types of uncertainty provided in EPA (PFOA), EPA (PFOS) and RIVM (GenX) documents.

**LOAEL to NOAEL & subchronic to chronic extrapolations were applied to some PODs but not all. EPA evaluated several potential PODs and these two uncertainty factors applied to some studies but not all.

RIVM does not offer a reference dose in these units because they assessed occupational exposure via inhalation.

## Clarification on risk assessment methods for GenX requiring further guidance from EPA and ATSDR

**Relative Source Contribution (RSC):** RSCs are important in risk assessment because they recognize that people are exposed to chemicals through drinking water, but they are also exposed through food, dust, soil, and air. For specific examples, the RIVM report shows significant emissions in one manufacturing scenario and shows that inhalation can be a relevant exposure route for members of a community near a GenX manufacturing plant. The EPA HAs for PFOA and PFOS consider the ubiquitous presence of these chemicals and use an RSC of 20% to allow for multiple exposure routes. GenX is a replacement for PFOA and the volume of GenX use and extent of potential widespread GenX occurrence is unknown. The RSC value commonly applied to organic chemicals is 20%, and that is the value we propose adopting for assessment of GenX.

**Uncertainty Factor for Interspecies Variability:** Interspecies variability in GenX toxicity is likely to be underestimated by the default value of 10. Mice and rat studies with GenX that were submitted for chemical registration and manufacturing were up to 300X different in rats and mice using the same test method. EPA's PFOA and PFOS drinking water health advisories used interspecies variability calculated up to a maximum of 2,100X (Table 3). Methods are needed to account for the high interspecies variability in GenX and more research is needed to provide an appropriate uncertainty factor value that is more specific to GenX.

## Clarification on request for health guidance value for other PFECAs



Residents in this community are requesting guidance on interpreting concentrations of GenX and other PFECA chemicals that were detected in their drinking water in 2013 and 2014. Additional testing is being performed to determine what concentrations are in their drinking water at this time. There is no health data available for these chemicals and it is expected that it could take years until more data will become available. Would it be appropriate to use the PFOA + PFOS health advisory of 70 ng/L until more research data can be collected and a more specific guidance can be offered?

# Appendix:

### EPA PFOA and PFOS drinking water health advisory calculations

Summary of risk assessment methods EPA used when developing drinking water health advisory levels for PFOA and PFOS (EPA 2016a, 2016b).

1) Animal studies with NOAELs and LOAELs were selected to use as points of departure (POD).
2) PODs were modeled to get human equivalent doses (HEDs).
    a. Part of the interspecies variability was accounted for in this step.
    b. Example PODs and corresponding HEDs are shown below in table 5-1 from the PFOA document.
3) HEDs were adjusted by uncertainty factors (UFs) to get reference doses (RfDs) and the most conservative RfD was selected for moving on to the next step.
    a. Values for UFs were multiplied to obtain $UF_{Total}$
        i. $UF_H$: Intraspecies variability=10
        ii. $UF_A$: Interspecies variability=3
        iii. $UF_L$: LOAEL to NOAEL extrapolation=10
        iv. $UF_S$: Subchronic to Chronic extrapolation=10
        v. $UF_D$: Database uncertainty did not apply
    b. $RfD = HED/UF_{Total}$
    c. Example HEDs and corresponding RfDs are shown below in table 5-2 from the PFOA document.
4) Exposure to the RfD was calculated and reported as a drinking water equivalent level (DWEL).
    a. DWEL=[RfD x bw]/DWI
        i. Where bw=body weight and DWI=drinking water equivalent
        ii. DWI/bw=0.054L/kg/day
5) DWEL was adjusted for the relative source contribution (RSC) from water in order to get a lifetime HA level.
    a. Lifetime HA = DWEL x RSC
    b. RSC used for both PFOA and PFOS was 20%

**Table 5-1. Human Equivalent Doses Derived from the Modeled Animal Average Serum Values**

| Study | Dosing duration days | NOAEL mg/kg/d | NOAEL Av serum mg/L | HED mg/kg/d | LOAEL mg/kg/d | LOAEL (Av serum) mg/L | HED mg/kg/d |
|---|---|---|---|---|---|---|---|
| DeWitt et al. (2008): mice; ↓ IgM response to SRBC | 15 | 1.88 | 38.2 | 0.0053 | 3.75 | 61.9 | 0.0087 |
| Lau et al. (2006): mice decreased ↓ pup ossification (m, f), accelerated male puberty | 17 | None | - | - | 1 | 38.0 | 0.0053 |
| Palazzolo et al. (1993); Perkins et al. (2004): rats; ↑liver weight/necrosis | 91 | 0.64 | 31.6 | 0.0044 | 1.94 | 77.4 | 0.0108 |
| Wolf et al. (2007): mice; GD 1–17 ↓Pup body weight | 17 | None | - | - | 3 | 77.9 | 0.0109 |
| Wolf et al. (2007): mice; GD 7–17 ↓Pup body weight[1] | 11 | None | - | - | 5 | 87.9 | 0.0123 |
| Butenhoff et al. (2004a): ↓ relative body weight/↑ relative kidney weight and ↑kidney: brain weight ratio in F0 and F1 at sacrifice | 84 | None | - | - | 1 | 45.9 | 0.0064 |

*Notes*:
Significance $p < 0.05$ or $p < 0.01$
m = male; f = female; SRBC = sheep red blood cell; IgM = immunoglobulin M; GD = gestation day
[1] serum from pups on PND 22

Table 5-1 from EPA Drinking Water Health Advisory for PFOA

**Table 5-2. Candidate RfDs Derived from the HEDs from the Pharmacokinetic Model Average Serum Values**

| POD | HED POD mg/kg/day | $UF_H$ | $UF_A$ | $UF_L$ | $UF_S$ | $UF_D$ | $UF_{total}$ | Candidate RfD mg/kg/day |
|---|---|---|---|---|---|---|---|---|
| $PK\text{-}HED_{NOAEL}$ Palazzolo et al. (1993)/Perkins et al. (2004) rats; ↑liver weight/necrosis | 0.0044 | 10 | 3 | - | - | - | 30 | 0.00015 |
| $PK\text{-}HED_{LOAEL}$ Wolf et al. (2007) GD1-17 mice; ↓Pup body weight | 0.0109 | 10 | 3 | 10 | - | - | 300 | 0.00004 |
| $PK\text{-}HED_{LOAEL}$ Wolf et al. (2007) GD 7-17 mice; ↓Pup body weight (serum from pups on PND 22) | 0.0123 | 10 | 3 | 10 | - | - | 300 | 0.00004 |
| $PK\text{-}HED_{NOAEL}$ DeWitt et al. (2008) mice; ↓ IgM response to SRBC | 0.0053 | 10 | 3 | - | 10 | - | 300 | 0.00002 |
| $PK\text{-}HED_{LOAEL}$ Lau et al. (2006) mice decreased ↓ pup ossification (m, f), accelerated male puberty | 0.0053 | 10 | 3 | 10 | - | - | 300 | 0.00002 |
| $PK\text{-}HED_{LOAEL}$ Butenhoff et al. (2004a) ↓ relative body weight/↑ relative kidney weight and ↑kidney: brain weight ratio in F0 and F1 at sacrifice | 0.0064 | 10 | 3 | 10 | - | - | 300 | 0.00002 |

*Notes*:
PK-HED = pharmacokinetic human equivalent dose; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestation day; IgM = immunoglobulin M; m = male; f = female; SRBC = sheep red blood cell; $UF_H$ = intraindividual uncertainty factor; $UF_A$ = interspecies uncertainty factor; $UF_S$ = subchronic to chronic uncertainty factor; $UF_L$ = LOAEL to NOAEL uncertainty factor; $UF_D$ = incomplete database uncertainty factor; $UF_{total}$ = total (multiplied) uncertainty factor

Table 5-2 from EPA Drinking Water Health Advisory for PFOA

**Table 5-1. Human Equivalent Doses Derived from the Modeled Animal Average Serum Values**

| Study | Dosing duration days | NOAEL mg/kg/d | NOAEL Av serum µg/mL | HED mg/kg/d | LOAEL mg/kg/d | LOAEL Av serum µg/mL | HED mg/kg/d |
|---|---|---|---|---|---|---|---|
| Seacat et al. (2003): male rat ↑ALT, ↑BUN | 98 | 0.34 | 16.5 | 0.0013 | 1.33 | 64.6 | 0.0052 |
| Luebker et al. (2005b): ↓ rat pup body weight | 84 | 0.1 | 6.26 | 0.00051 | 0.4 | 25 | 0.002 |
| Luebker et al. (2005a): ↓ rat pup body weight | 63 | None | None | None | 0.4 | 19.9 | 0.0016 |
| Luebker et al. (2005a): rat ↓ maternal body weight, gestation length, and pup survival | 63 | 0.4 | 19.9 | 0.0016 | 0.8 | 39.7 | 0.0032 |
| Butenhoff et al. (2009): rat DNT (↑motor activity; ↓habituation) | 41 | 0.3 | 10.4 | 0.00084 | 1.0 | 34.6 | 0.0028 |
| Lau et al. (2003): ↓rat pup survival; ↓maternal and pup body weight | 19 | 1.0 | 17.6 | 0.0014 | 2.0 | 35.1 | 0.0028 |

*Notes:*
ALT = alanine transaminase; BUN = blood urea nitrogen; DNT = developmental neurotoxicity; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; HED = human equivalent dose

Table 5-1 from EPA Drinking Water Health Advisory for PFOS

**Table 5-2. Candidate RfDs Derived from HEDs from the Pharmacokinetic Model Average Serum Values**

| POD | HED POD mg/kg/day | $UF_H$ | $UF_A$ | $UF_L$ | $UF_S$ | $UF_D$ | $UF_{total}$ | Candidate RfD mg/kg/day |
|---|---|---|---|---|---|---|---|---|
| (Seacat et al. 2003): male rat NOAEL for ↑ALT, ↑BUN | 0.0013 | 10 | 3 | 1 | 1 | 1 | 30 | 0.00004 |
| PK-HED (Lau et al. 2003): rat, NOAEL for ↓ pup survival and body weight | 0.0014 | 10 | 3 | 1 | 1 | 1 | 30 | 0.00005 |
| PK-HED (Butenhoff et al. 2009): rat, NOAEL for ↑motor activity ↓habituation | 0.00084 | 10 | 3 | 1 | 1 | 1 | 30 | 0.00003 |
| PK-HED (Luebker et al. 2005b): rat, NOAEL for ↓pup body weight | 0.00051 | 10 | 3 | 1 | 1 | 1 | 30 | 0.00002 |
| PK-HED (Luebker et al. 2005a): rat, NOAEL for ↓pup survival | 0.0016 | 10 | 3 | 1 | 1 | 1 | 30 | 0.00005 |
| PK-HED LOAEL (Luebker et al. 2005a): rat, LOAEL for ↓pup body weight | 0.0016 | 10 | 3 | 3 | 1 | 1 | 100 | 0.00002 |

*Notes:*
PK-HED = pharmacokinetic human equivalent dose; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; $UF_H$ = intra-individual uncertainty factor; $UF_A$ = interspecies uncertainty factor; $UF_S$ = subchronic to chronic uncertainty factor, $UF_L$ = LOAEL to NOAEL uncertainty factor; $UF_D$ = incomplete database uncertainty factor; $UF_{total}$ = total (multiplied) uncertainty factor

Table 5-2 from EPA Drinking Water Health Advisory for PFOS

## Resources

A collection of tests using OECD and EPA standardized methods were submitted for product registration in the EU and US, and these studies are discussed by many groups in different ways.

1) Very large reports of raw data can be acquired through Chemours by requesting from

2) Summaries on the European Chemical Agency (ECHA) Website. Navigate the test types on the left side of the webpage and use the pull-down button at the top of the page to move through studies 001, 002, etc. https://echa.europa.eu/registration-dossier/-/registered-dossier/2679/1
3) RIVM letter 2016 is an assessment from a European group focused on risk to a community in proximity to a GenX manufacturing facility from inhalation exposure. An interspecies uncertainty factor of 66 is applied for kinetics alone.
4) EPA 2008 Consent order contains a point of departure selected at that time.
5) WV DEP Consent order contains a point of departure selected at that time.
6) Peer reviewed literature by Caverly Rae et al 2015 covers OECD 453.
7) Peer reviewed literature Gannon et al 2016 covers kinetics and metabolism studies also on the ECHA website.

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**To:** Allison, Rose[Allison.Rose@epa.gov]; Doa, Maria[Doa.Maria@epa.gov]; Krasnic, Toni[krasnic.toni@epa.gov]; EL-Zoobi, Majd[El-Zoobi.Majd@epa.gov]; Aubee, Catherine[Aubee.Catherine@epa.gov]; Vendinello, Lynn[Vendinello.Lynn@epa.gov]; kemper.carol@epa.gov[kemper.carol@epa.gov]; Tobias, David[Tobias.David@epa.gov]; Benson, Amy[Benson.Amy@epa.gov]; George, Verne[George.Verne@epa.gov]; Mitchell, Ken[Mitchell.Ken@epa.gov]; sheila.holman@ncdenr.gov[sheila.holman@ncdenr.gov]; linda.culpepper@ncdenr.gov[linda.culpepper@ncdenr.gov]; Toney, Anthony[Toney.Anthony@epa.gov]; Bookman, Robert[Bookman.Robert@epa.gov]; Banister, Beverly[Banister.Beverly@epa.gov]
**Cc:** JOHNSON, MICHAEL E[MICHAEL.E.JOHNSON@chemours.com]
**From:** O'KEEFE, KATHLEEN E
**Sent:** Wed 7/12/2017 8:16:58 PM
**Subject:** Chemours web conference instructions Thursday July 13 at 1:00 pm

The web conference instructions are below. Please note you can join 10 minutes prior to the start of the meeting. After you register an access link will be provided by AT&T.

Thanks, Kathy

**Kathleen O'Keefe**
Chemours Product Sustainability Director

Mobile

Your web conference has been scheduled.

**Title**: Chemours Web Conference

**Date**: Thursday, July 13, 2017

**Time**: 1:00 PM - 2:00 PM Eastern Time

## Participant Instructions

**Web Link:** A participant may register for the conference at after which s/he will receive an email containing a personalized access link.